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Personalized Estimate of Chemotherapy-Induced Nausea and Vomiting: Development and External Validation of a Nomogram in Cancer Patients Receiving Highly/Moderately Emetogenic Chemotherapy

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Abstract: Chemotherapy-induced nausea and vomiting (CINV) is presented in over 30% of cancer patients receiving highly/moderately emetogenic chemotherapy (HEC/MEC). The currently recommended antiemetic therapy is merely based on the emetogenic level of chemotherapy, regardless of patient's individual risk factors. It is, therefore, critical to develop an approach for personalized management of CINV in the era of precision medicine.

A number of variables were involved in the development of CINV. In the present study, we pooled the data from 2 multi-institutional investigations of CINV due to HEC/MEC treatment in Asian countries. Demographic and clinical variables of 881 patients were prospectively collected as defined previously, and 862 of them had full documentation of variables of interest. The data of 548 patients from Chinese institutions were used to identify variables associated with CINV using multivariate logistic regression model, and then construct a personalized prediction model of nomogram; while the remaining 314 patients out of China (Singapore, South Korea, and Taiwan) entered the external validation set. C-index was used to measure the discrimination ability of the model.

The predictors in the final model included sex, age, alcohol consumption, history of vomiting pregnancy, history of motion sickness, body surface area, emetogenicity of chemotherapy, and antiemetic regimens. The C-index was 0.67 (95% CI, 0.62–0.72) for the training set and 0.65 (95% CI, 0.58–0.72) for the validation set. The C-index was higher than that of any single predictor, including the emetogenic level of chemotherapy according to current antiemetic guidelines. Calibration curves showed good agreement between prediction and actual occurrence of CINV.

This easy-to-use prediction model was based on chemotherapeutic regimens as well as patient's individual risk factors. The prediction accuracy of CINV occurrence in this nomogram was well validated by an independent data set. It could facilitate the assessment of individual risk, and thus improve the personalized management of CINV.

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Abbreviations: 5HT3-RA = 5-hydroxytryptamine$_3$ receptor antagonists, BSA = body surface area, CI = confidence interval, CINV = chemotherapy-induced nausea and vomiting, ESMO = European Society for Medical Oncology, HEC = highly emetogenic chemotherapy, MASCC = Multinational Association for Supportive Care in Cancer, MEC = moderately emetogenic chemotherapy, NCCN = National Comprehensive Cancer Network, NK1-RA = Neurokinin-1 receptor antagonists, PrACTICE = Pan Australasian Chemo-Therapy InduCed Emesis burden study, PS = performance status, QOL = quality of life, VP = vomiting pregnancy.

INTRODUCTION

Chemotherapy-induced nausea and vomiting (CINV) is an obvious and distressing adverse event associated with cancer treatment, which compromised both therapeutic effects and patient quality of life (QOL).[1–3] Despite the development of modern antiemetic therapy,[4] including the serotonin antagonists (5HT3-RA) and neurokinin-1 receptor antagonists (NK1-RA), more than 30% of cancer patients still experience CINV after receiving highly/moderately emetogenic chemotherapy (HEC/MEC).[5–8] CINV is stubborn to treat after its initial outbreak, as it is poorly responsive to salvage therapy and increases the probability of subsequent CINV onsets.[9,10] However, the current recommendations in antiemetic guidelines are merely based on the emetogenic levels of chemotherapy,[11,12] regardless of patient's individual conditions. Therefore, it is critical to develop an approach of personalized management of CINV based on the individual risk prediction, which could guide more effective antiemetic prophylaxis prior to chemotherapy.

CINV is a complicated condition, whose development involves a number of variables.[1] Female, young age, low alcohol consumption, higher emetogenicity of chemotherapy,

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presence of anxiety and fatigue, and even patient's expectation of CINV have been implicated to increase the risk of CINV.[13,14] To date, several mathematical prediction models have been developed to calculate patients' risks of CINV, which stratified patents into high- or low-risk groups based on their risk scores.[15–18] However, the complex arithmetic resulted in poor feasibility, and thus limited their application in clinical practice. Furthermore, it remains not enough to stratify patients by risk grouping in the era of precision medicine; healthcare professionals need more accurate approach to individually assess each patient's risk of CINV development in daily practice.

Nomogram has been employed to quantify the probability of a clinical event by combining multiple variables associated.[19,20] Its user-friendly graphical interfaces promote the popularity of nomogram in clinician's decision-making. The present study aimed to develop and externally validate a pragmatic nomogram that individually predicts the occurrence of CINV in patients receiving HEC/MEC. The patient data were obtained from a large-scale randomized, multicenter, phase III trial of CINV prevention in China (Aprepitant P169 study)[21] and an observational study of CINV burden in multiple Asian Pacific countries (PrACTICE study).[7]

METHODS

Patient Selection

The recruited patients of this analysis were from 2 independent studies of CINV prevention in Asian countries. In the P169 study,[21] a total of 412 patients from 16 investigational centers were evaluable for CINV in the first cycle of chemotherapy, thus enrolled into this analysis. All the patients were chemo-naive and randomly assigned to receive NK1-RA (n = 209) or placebo (n = 212) combined with 5HT3-RA and corticosteroid for prevention of CINV due to HEC. While in the PrACTICE study, [7] a total of 684 patients in 6 countries were documented of CINV prevention after a single-day HEC or MEC treatment in daily practice. Considering the therapeutic disparities among different countries as described previously,[22] we only recruited the 486 patients from China (n = 153), Singapore (n = 57), South Korea (n = 151), and Taiwan (n = 125) in this study. All of the patients enrolled were from East-Asian population.

To construct a nomogram including both HEC and MEC populations, we pooled all subjects from China as the training set, including patients in P169 study (HEC population) and those in PrACTICE study (HEC and MEC populations). The data of the remaining patients out of China were used for external validation of the nomogram. Both the studies had been approved by institutional review boards of each participating institution, so the present analysis got a waiver of additional ethical approval.

Factor Collection

To explore the predictors of CINV occurrence, we examined the following demographic and clinical variables of interest: sex, age, body surface area (BSA), alcohol consumption, history of vomiting pregnancy (VP), history of motion sickness, emetogenicity of chemotherapy, performance status (PS), and antiemetic regimens.

Based on sex and history of VP, the population was categorized as male, female without VP, and female with VP. Alcohol consumption was classified as less than or $\geq$1 time per week on average in consuming alcoholic drinks. The emetogenicity of chemotherapy was classified as highly/moderately emetogenic chemotherapy (HEC/MEC) according to MASCC/ESMO 2010 Guidelines.[11] The antiemetic regimens were categorized, consistent with the antiemetic options in MASCC/ESMO 2010 Guidelines, as single-agent therapy (5HT3-RA), doublet therapy (5HT3-RA and corticosteroids), and triplet therapy (NK1-RA, 5HT3-RA, and corticosteroids).

Although some other variables might be implicated in the occurrence of CINV according to previous reports, such as anxiety, fatigue, and anticipation of CINV development;[14] they were excluded from our study because these subjective variables are poorly accessible in clinical practice. Besides, the impact of these subjective variables on CINV development was very limited compared with other demographic and clinical variables.[13] Their roles in the nomogram would probably be compromising the feasibility rather than increasing prediction accuracy.

Statistical Analysis

Complete response was adopted as an indicator of successful prevention of CINV, which was defined as no vomiting and no rescue therapy during the overall 120 hours postchemotherapy. Although mild nausea might present in patients with complete response, it remains an important goal for antiemetic prophylaxis to protect patients from negative impacts due to CINV.[11] To identity predictors of CINV occurrence, multivariate logistic regression analysis was used to test the association between complete response and variables of interest listed above.

The methods used to develop the nomogram were according to those previously described.[20,23] For the training cohort, we used the bootstrapping method to validate internally. The generalization of the nomogram was confirmed by external validation using the validation set. The predictive accuracy (discrimination) of the nomogram was measured via a concordance index (c-index). Calibration plot was drawn to compare how well the predicted probabilities from the nomogram matched the actual probabilities. Bootstraps resample methods with 100 repetitions were used for these activities.

All analyses were carried out using SPSS version 20 (IBM Corp, Armonk, NY) and R 2.14.1 software with Package Hmisc version 3.4-2. In all statistical analyses, a P value of <0.05 was considered significant.

RESULTS

In total, 881 patients were collected in the present study, with 565 for nomogram development and 316 for validation. After excluding patients with missing data on BSA (n = 7), alcohol consumption (n = 7), CINV evaluation (n = 2), and history of motion sickness (n = 1), 548 subjects were enrolled to the training set (N = 548), including 397 patients in P169 study (HEC), and 151 in the PrACTICE study (77 HEC and 74 MEC); their demographic and other baseline characteristics are listed in Table 1. Excluding 2 patients without information of alcohol consumption, a total of 141 cases with HEC and 173 cases with MEC in the PrACTICE study were included in the validation set (N = 314), including 56 in Singapore, 142 in South Korea, and 116 in Taiwan.

CINV event was presented in 37.2% of patients (204/548) in the training set, with 40.0% in HEC population (180/474) and 32.4% in MEC population (24/74); while in the validation set, it was 28.4% (40/141) and 23.1% (40/173), in HEC and MEC populations, respectively.

TABLE 1. Demographic and Clinical Variables of the Training Set and External Validation Set

	Training Set (N = 548)		External Validation Set (N = 314)	
Variables	**n**	**%**	**n**	**%**
Sex				
Male	334	60.9	138	43.9
Female	214	39.1	176	56.1
Age, yr				
Median (range)	55 (20–77)		57 (22–85)	
PS score				
0	318	58.0	173	55.1
1–2	230	42.0	141	44.9
BSA				
Median (range)	1.67 (1.18–2.18)		1.71 (1.31–2.19)	
Primary cancer diagnosis				
Lung	327	59.7	70	22.3
Breast	50	9.1	84	26.8
HNSCC	34	6.2	8	2.5
Colon	32	5.8	61	19.4
Gynecologic	24	4.4	18	5.7
Stomach	20	3.6	15	4.8
Others	62	11.3	58	18.5
Alcohol consumption				
<1 per week	461	84.1	275	87.6
>=1 per week	87	15.9	39	12.4
History of motion sickness				
Yes	23	4.2	53	16.9
No	525	95.8	261	83.1
History of VP in female				
Yes	48	22.4	81	51.6
No	166	77.6	76	48.4
Emetogenicity of chemotherapy				
HEC	474	86.5	141	44.9
MEC	74	13.5	173	55.1
Antiemetic therapy				
Single-agent	40	7.3	25	8.0
Doublet	309	56.4	206	65.6
Triplet	199	36.3	83	26.4

BSA = body surface area, Doublet = 5HT3-RA+corticosteroid, HEC = highly emetogenic chemotherapy, HNSCC = head and neck squamous cell carcinoma, MEC = moderately emetogenic chemotherapy, PS = performance status; Single-agent = 5-HT3 receptor antagonist (5HT3-RA), Triple = 5-HT3RA+corticosteroid+ neurokinin-1 receptor antagonist (NK-1RA), VP = vomiting pregnancy.

Establishment of CINV Nomogram

First, we assessed the predictive value of each variable through logistic regression. Table 2 lists the selected variables with odds ratio and *P* values: sex (with females stratified by history of VP) ($P < 0.001$), age ($P = 0.339$), alcohol consumption ($P = 0.108$), history of motion sickness ($P = 0.847$), BSA ($P = 0.079$), emetogenicity of chemotherapy ($P = 0.045$), and antiemetic regimens ($P = 0.012$). We finalized a nomogram that integrated all the predictors (Figure 1), in which the most significant predictors were: sex by VP, emetogenicity of chemotherapy, and antiemetic regimens. The C-index for CINV prediction was 0.67 (95% CI, 0.62–0.72) in this nomogram. The calibration plot for the probability of CINV showed an optimal agreement between the prediction by nomogram and actual observation (Figure 2A).

TABLE 2. Selected Variables According to Multivariate Logistic Regression Model

Variables	Odds Ratio	95% CI	*P* Value
Sex and VP			
Male	Ref		
Female without VP	1.87	1.18–2.97	<0.01
Female with VP	3.96	1.93–8.10	<0.01
Age, yr	0.99	0.97–1.01	0.34
BSA, m^2	0.32	0.09–1.14	0.08
Alcohol consumption			
No	Ref		
Yes	0.61	0.34–1.11	0.11
Motion sickness			
No	Ref		
Yes	0.91	0.36–2.33	0.85
Emetogenic level			
MEC	Ref		
HEC	1.86	1.02–3.40	0.04
Antiemetic therapy			
Single-agent	Ref		
Doublet	0.89	0.43–1.86	0.76
Triplet	0.49	0.22–1.08	0.08

BSA = body surface area, CI = confidence interval, Doublet = 5HT3-RA plus corticosteroid, MEC/HEC = moderately/highly emetogenic chemotherapy, Ref = reference, Single-agent = 5HT3 receptor antagonist (5HT3-RA), Triplet = 5HT3-RA, corticosteroid, and neurokin-1 receptor antagonist (NK1-RA), VP = vomiting pregnancy.

As several prediction variables were not statistically significant in the training set, we performed another developing of nomogram including only those significantly associated with CINV (sex by VP, emetogenicity of chemotherapy, and antiemetic regimens). The C-index for CINV prediction was 0.58 (95% CI, 0.53–0.63), which was less than the nomogram including all predictors ($P = 0.02$).

External Validation of the CINV Nomogram

As previously reported, clinical data from other countries were the most stringent test population for model validation.[24] Using the subjects from Singapore, South Korean, and Taiwan in the PrACTICE study, external validation was performed subsequently. Figure 2B shows the calibration plot of the nomogram.

The *X*-axis is the predicted CINV occurrence probability estimated by the nomogram, and the *Y*-axis is the actual rates of patients with CINV development. The solid line represents the ideal reference line where predicted CINV corresponds to the actual outcome, and the dash lines represent a 10% margin of error. The actual CINV corresponded closely to the predicted development and was always within the 10% margin of error. The calibration plot for the probability of CINV showed a good agreement between the prediction by nomogram and actual observation (Figure 2B). The C-index for CINV prediction was 0.65 (95% CI, 0.58–0.72). Furthermore, we compared the discrimination of the present nomogram with that of the MASCC/ESMO 2010 Guidelines classification (HEC/MEC). The discrimination of our nomogram was superior to that of

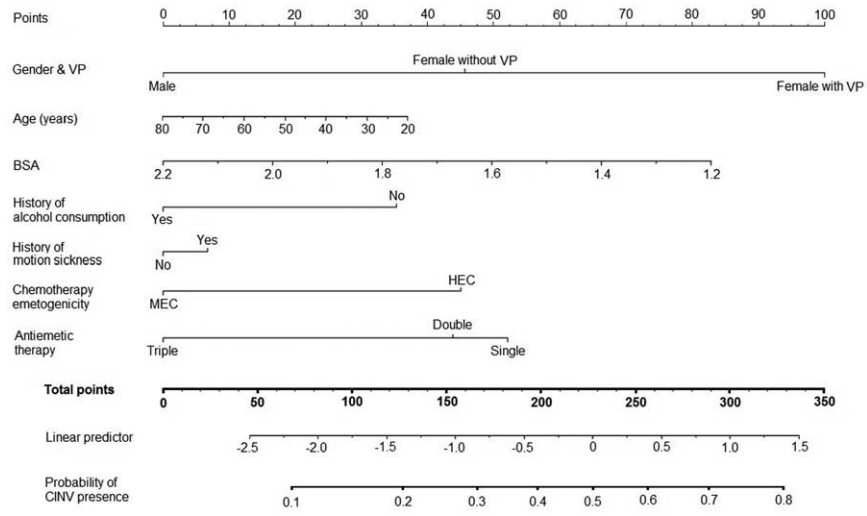

FIGURE 1. Prediction nomogram of CINV in cancer patients receiving HEC/MEC treatment. BSA = body surface area; CINV = chemotherapy-induced nausea and vomiting; HEC/MEC = highly/moderately emetogenic chemotherapy; VP = vomiting pregnancy.

the current chemotherapy emetogenicity classification (C-index = 0.54; 95% CI, 0.46–0.61).

DISCUSSION

We have developed and externally validated a practical nomogram that is able to predict the individual risk of CINV occurrence in cancer patients receiving HEC/MEC treatment. This tool is easy to use thanks to the friendly interface and visual graphics, instead of complex mathematical calculation. Personalized estimation of patient's risk of CINV development could help healthcare professionals prevent this common adverse event, such as prescribing appropriate antiemetic agents or selecting chemotherapeutic regimens. On the other hand, identification of patients with low risk might avoid overtreatment in the CINV prophylaxis according to the current antiemetic guidelines.

CINV is a persistent issue in the management of cancer patients receiving chemotherapy, especially the HEC and MEC.[5,25] The problem has been highlighted by the complicated mechanisms of CINV development,[26] the following refractory situation after its initial onset,[10] as well as the underestimation from clinicians.[7,27] Therefore, an approach that individually predicts patient's risk is critical to guide the precision medicine in the management of CINV. In the present study, we enrolled patients from 2 high-quality clinical studies on CINV prevention in multiple countries. Using a practical tool of nomogram, we built a prediction model for personalized estimate of CINV development, which demonstrated an accuracy of 0.67 in overall patients revealed by the C-index. Importantly, this nomogram was validated by independent data from an observational study of CINV prevention, which reflected the real world of clinician's daily practice and patients CINV burden. Furthermore, the wide distribution of investigational sites (14 sites in 3 countries) in the validation set ensured this nomogram a large extent of applicability, which was deemed the most stringent validation of prediction models.[24]

Previous studies have revealed that earlier CINV onset would increase the probability of CINV in subsequent cycles of

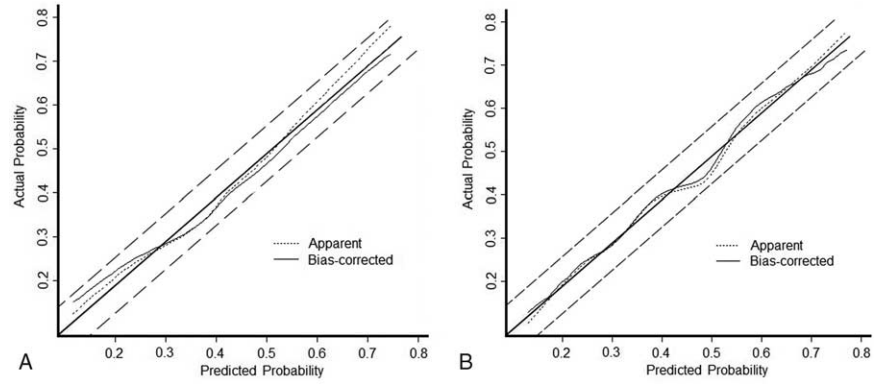

FIGURE 2. Calibration plots for the probability of CINV in nomogram and actual observation in the training set (A) and in external validation set (B). The *X*-axis represents the predicted CINV probabilities estimated by the nomogram, and the *Y*-axis is the actual rates of CINV development. The solid straight line means the ideal reference line where predicted CINV corresponds to the actual outcome, and the dashed straight lines represent a 10% margin of error.

chemotherapy,[9,18,28] suggesting that the best "treatment" of CINV is optimal prophylaxis prior to the first dosing of chemotherapy. In our study, the development and prediction of CINV was based on patient's first cycle of HEC or MEC treatment, which was supported by the importance of initial CINV prevention. Although the antiemetic guideline consistency is important for CINV prevention,[6,8] however, once evaluated his or her CINV risk by this nomogram, a patient could receive modified antiemetic regimens beyond the stereotyped medications according to current guidelines. Besides the 5HT3-RA, NK1-RA, and corticosteroid, some more antiemetic agents have been demonstrated effective in the CINV prevention, such as dopamine antagonists, ginger, histamine blockers, proton pump inhibitors, and so on.[29–31] Of these, olanzapine has been studied in a wide range of population, which showed additional CINV prevention when combined with standard triplet antiemetic therapy.[29] For those with high risk of CINV, clinicians should consider a modified antiemetic regimen with additional use of these unconventional antiemetic agents. Besides, some other actions could be taken to prevent CINV, such as psychological intervention, lifestyle adjustment, or symptoms control on fatigue or anxiety, as described in NCCN guidelines.[12,32] The nomogram is also helpful for those who have low risk of CINV but presented contradiction toward recommended agents, such as corticosteroid.[33]

As to predictors in the nomogram, we did not include all the variables potentially associated with CINV in the present study. Some subjective variables may impair the feasibility of prediction model in clinical practice due to poor repeatability as well as limited impacts on CINV, such as anxiety and fatigue.[14] Besides, several variables in the final nomogram were not statistically significantly associated with CINV in our training set; however, these risk factors have been substantially studied and confirmed previously. The inclusion of these predictors was suggested by a superior prediction accuracy revealed by the C-index (0.67 vs. 0.62). The lack of correlations might result from limited sample size and positive cases with VP and motion sickness history in the training set. Interestingly, the BSA played an important role in the development of CINV in our study, although the mechanisms underlying were not well defined.

Despite many advantages of this prediction nomogram, further work remains needed to make it more applicative in future clinical practice. First, this nomogram only predicts the CINV due to the first cycle of HEC/MEC treatment. Dynamic prediction is necessary for effective CINV management, as the probability of its occurrence would increase with the continuation of chemotherapy.[34] Second, predictors and their contribution to CINV may be different in acute phase (<24 hours) and delayed phase (24–120 hours) after chemotherapy. The mechanisms of CINV development during these phases are distinct according to recent research;[26,35] so it is necessary to figure out such differences in CINV prediction in future studies, which may increase the accuracy of CINV prediction. Furthermore, all the patients in our study were from Asian countries, so its applicability should be further investigated in other ethnic populations. Nevertheless, this well-validated nomogram was quite convincing and could help the personalized management of CINV in clinical practice.

To conclude, the development and validation of a prediction approach is critical in the personalized management of CINV. The nomogram we presented here is an ease-to-use tool, which could help healthcare professionals to estimate individual risk of CINV development and then make proper clinical decisions for cancer patients receiving HEC/MEC treatment. Further studies are warranted to improve our understanding of CINV development as well as personalized prophylaxis of CINV.

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